Potentiation of Insulin Secretion after Oral, Duodenal and Ileal Glucose Administration in Rats

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POTENTIATION OF INSULIN SECRETION AFTER ORAL, DUODENAL AND ILEAL GLUCOSE ADMINISTRATION IN RATS.

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Glucose-induced insulin secretion is potentiated by enteric factors. The aim of the present study was to investigate the relative contribution of factors from different areas of the intestinal tract on glucose-stimulated insulin release. Male Wistar rats (n=6) were provided with permanent catheters in atrium, duodenum (D) and ileum at 40 cm (I-1) and at 15 cm (I-2) distance from caecum. Blood was sampled via one of two heart catheters and analyzed for glucose and insulin. Graded intravenous glucose infusions given via another heart catheter resulted in dose-dependent increments of blood glucose and plasma insulin responses. After spontaneous oral ingestion of glucose loads of 150 mg and 750 mg the maximal blood glucose increments were similar, 1.2 ± 0.1 and 1.2 ± 0.1 mmol/L and insulin 41 ± 8 and 72 ± 8 mU/L respectively. After glucose administration into duodenum these values were for glucose 2.0 ± 0.17 and 2.5 ± 0.17 mmol/L and insulin 132 ± 18 and 184 ± 22 mU/L respectively. For I-1, these values were for glucose 1.7 ± 0.23 and 2.2 ± 0.17 mmol/L and insulin 90 ± 16 and 130 ± 18 mU/L respectively. No significant glucose increments were seen after I-2 infusion of only 150 mg of glucose whereas insulin increased from 52 ± 6 to 82 ± 9 mU/L ($p < 0.05$) The insulinogenic index of integrated responses measured as the area under the curve from 0-20 minutes, was 1.8 times higher for oral, 2.3 for duodenal and 2.2 for I-1 administration than during intravenous glucose infusion. These results indicate that alimentary glucose potentiates insulin secretion to almost the same extent independent of the site of intestinal glucose absorption.

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OPPOSITE EFFECTS OF GLUCOSE AND 2-KETOISOCAPROATE ON INSULIN RELEASE FROM THE PERFUSED PANCREAS OF GLUCOSE-INFUSED RATS

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A typical feature of B-cell glucotoxicity consists in a paradoxical inhibition of insulin secretion in response to a rapid rise in glycaemia. This might be due, in part at least, to inactivation of phosphorylase, so that inhibition of glycogenolysis would transiently decrease glycolytic flux despite enhanced utilization of exogenous glucose. To further explore such a hypothesis, the effect of glucose was compared to that of 2-ketoisocaproate in perfused pancreases removed from rats first infused for 48 hours with a hypertonic solution of glucose. In this model, a fall in glucose concentration from 16.7 to 2.8 mmol/l provoked a paradoxical stimulation of insulin output. A further rise in hexose concentration to 12.8 mmol/l caused an immediate suppression of the paradoxical secretory response. On the contrary, the administration of 2-ketoisocaproate (10 mmol/l), at the low concentration of glucose, caused a biphasic enhancement of insulin release, comparable to that otherwise found in the pancreas of euglycemic rats. The opposite effects of glucose and 2-ketoisocaproate reinforce the view that the paradoxical secretory response to the hexose coincides with a paradoxical change in glycolytic flux, rather than primary alteration of the coupling between ATP generation and more distal events in the secretory sequence.

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ROLE OF GLUCOSE METABOLISM IN GLUCOSE-INDUCED SENSITIZATION/DESENSITIZATION OF INSULIN SECRETION

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The role of glucose metabolism in glucose-induced sensitization/desensitization of insulin secretion was studied. A change in glucose concentration from 5.5 to 16.7 mmol/l during 22-24 h of pre-exposure of mouse islets in TCM 199 culture medium (0.26 mmol/l Ca^{2+}) led to sensitization of insulin secretion, and caused an increase in glucose(16.7 mmol/l)-induced insulin secretion from 102 ± 30(5) to 231 ± 37(5) ng/h per 25 islets (means ± SEM(n)) ($P<0.005$). In islets pre-exposed to 5.5 and 16.7 mmol/l glucose, glucose utilization (D-[5-^{3}H]glucose conversion to ^3HOH) at 16.7 mmol/l glucose was determined to 2126 ± 51(3) and 2462 ± 160(3) pmol/2 h per 25 islets, respectively ($P>0.05$). Glucose oxidation (D-[U-^{14}C]glucose oxidation to $^{14}CO_2$) at 16.7 mmol/l glucose amounted to 805 ± 40(5) and 846 ± 154(5) pmol/2 h per 25 islets ($P>0.05$) in islets pre-exposed to 5.5 and 16.7 mmol/l glucose, respectively. At 1.26 mmol/l Ca^{2+} in TCM 199 medium, a change in glucose concentration from 5.5 to 16.7 mmol/l led to desensitization and a reduction in glucose(16.7 mmol/l)-induced insulin secretion from 115 ± 28(5) to 64 ± 20(5) ng/h per 25 islets ($P<0.005$). In these islets, glucose utilization at 16.7 mmol/l glucose was 2373 ± 218(3) and 2594 ± 218(3) pmol/2 h per 25 islets ($P>0.05$), and glucose oxidation was determined to 1002 ± 116(4) and 901 ± 207(4) pmol/2 h per 25 islets ($P>0.05$) after pre-exposure to 5.5 and 16.7 mmol/l glucose, respectively. In conclusion, these data suggest that glucose-induced sensitization/desensitization of insulin secretion may occur independently of concomitant changes in glucose metabolism.

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STIMULATION OF INSULIN SECRETION BY PRENYLCYSTEINE ANALOGS MIMICKING THE COOH-TERMINUS OF GTP-BINDING PROTEINS

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Most GTP-binding proteins (G-proteins) contain an *S*-prenylated C-terminal cysteine whose carboxyl group is reversibly methylated. We investigated the putative regulatory role of this reaction in insulin secretion by introducing into streptolysin-O permeabilized HIT-T15 cells prenylcysteine analogs that are competitive substrates for the methyltransferases. We found that *N*-acetyl-*S*-geranylgeranyl-cysteine (AGGC), at 50μM, doubled both basal (100nM Ca^{2+}) and stimulated (10μM Ca^{2+} or 100μM GTP[S]) insulin release. The effect of AGGC was dose-dependent, reversible and required ATP. *N*-acetyl-*S*-farnesyl-cysteine (AFC) was less potent while *N*-acetyl-*S*-geranyl-cysteine was inactive. These results correlate with the efficacy with which these prenylcysteine analogs inhibit methyltransferases in HIT-T15 cell fractions. However, the methyl ester derivative of AFC, that does not affect methylation of G-proteins, was as potent as AGGC in stimulating exocytosis. Similarly, *S*-adenosyl-homocysteine, a general inhibitor of methylation reactions, did not alter basal or GTP[S] triggered secretion but inhibited Ca^{2+}-induced insulin release. A synthetic peptide corresponding to the putative effector binding region of the G-protein rab3 (rab3AL), at 50μM, had the same effect as AGGC on insulin release. rab3AL and AGGC were not additive on secretion, suggesting a common mechanism of action. These results indicate that prenylcysteine analogs trigger exocytosis by competing with an acceptor protein interacting with the C-terminus of G-proteins rather then by inhibiting methyltransferases.